The emergence of novel targets and innovative therapeutics continues to improve the treatment and outcomes for patients with hematologic malignancies. After the tremendous impact on survival for patients with chronic myelogenous leukemia (CML) observed with the development of imatinib, the bar has been raised for other agents being tested in these types of cancer. Recent scientific meetings and publications have shown impressive new data for treating chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), multiple myeloma, and other blood disorders.

**Bendamustine (Treanda, Cephalon)** has recently been approved for the treatment of patients with CLL and relapsed indolent lymphoma. Results of a randomized international study comparing bendamustine vs. chlorambucil revealed a doubling in progression-free survival (PFS) (20 months vs. 10 months) in untreated CLL favoring the bendamustine arm. The combination of bendamustine and rituximab in relapsed CLL yielded a 77% overall response rate (ORR) and a 14% complete response rate (CR) in a group of 81 patients. Toxicities with bendamustine center around myelosuppression and are generally reversible and manageable.

**Lenalidomide (Revlimid, Celgene)** produced a 54% ORR in 35 elderly patients (older than 65 years; median age 72) with untreated CLL. A total of 17 patients (44%) actually experienced a tumor flare manifested by bone pain, fever, and an increased white blood cell count, but no tumor lysis syndrome resulted. Studies of lenalidomide in the salvage therapy of CLL are also under way, with preliminary reports of molecular CRs seen in a few patients. Clearly, this immunomodulatory agent has provocative activity in multiple hematologic malignancies.

**Ofatumumab**, a fully human monoclonal IgG1 antibody targeting a novel epitope of the CD 20 molecule on B cells, demonstrated a 50% ORR among 26 patients with recurrent and refractory CLL. Infections occurred in 9% of patients, including one fatal interstitial pneumonitis.

**Flavopiridol (Alvocidib)**, a cyclin-dependent kinase inhibitor, continues to be explored in CLL. In a phase 2 study of 42 patients with recurrent and refractory cytogenetically high-risk CLL, flavopiridol produced a 45% ORR with a median PFS of 11 months. Tumor lysis syndrome was seen biochemically in half the patients, including two that developed grade 3/4 renal failure. A larger report of
117 patients with CLL/SLL (small lymphocytic lymphoma) describing durable remissions added to the growing data confirming flavopiridol’s activity in this disease. The study of CML has begun to focus on the resistant and mutated populations still needing treatment despite the incredible successes of imatinib, dasatinib, and nilotinib.

In particular, the T315i mutation appears to be responsible for the majority of these resistant or recurrent populations. A partial list of these agents includes AP24534 (Ariad), SGX-393 (Lilly), XL228 (Exelixis), INNO-406 (CytRx), and omacetaxine (homoharringtonine, Chemgenex). INNO-406, an oral dual BCR-ABL and lyn kinase inhibitor, demonstrated a 35% response rate among 56 patients resistant to imatinib.

Omacetaxine was evaluated subcutaneously in 50 patients failing prior imatinib, and in addition to a complete cytogenetic response in 20% of the group, the T315i mutation was decreased below the limit of detection in 60% of patients. The understanding of the molecular biology of CML has allowed innovative therapeutics to be developed, and the resulting impact on the patients has been spectacular.

Myelodysplastic syndrome describes a group of disorders beginning to be helped through the study of several new agents. Decitabine and azacytidine have recently been approved for MDS, and clinical trials evaluating new combinations have begun, including a program of azacytidine and lenalidomide. Clofarabine, a second-generation deoxycadenosine analog, can be administered orally and intravenously. In a trial of 50 patients, half dosed with each schedule and half with prior hypomethylator therapy, an ORR of 46% including 30% CRs was demonstrated. Interestingly, of almost 4,000 abstracts presented at the American Society of Hematology’s 2008 meeting (ASH 2008), only 3% involved the study of MDS, despite affecting 75,000 patients a year.

In the treatment of aggressive and indolent non-Hodgkin’s lymphoma, a study of adjuvant radiotherapy with irbritumomab (Zevalin, CH1) in stage 1 and 2 diffuse large B cell lymphoma was performed in 40 patients, yielding a two-year PFS of 91% (just three events observed) and a 95% overall survival. The role and timing of the use of radiotherapeutics remain debatable, but they are clearly an active weapon against lymphomas. Maintenance rituximab (375 mg/m² q three months until progression or two years of therapy) vs. observation in 465 patients improved median PFS from 1.3 years to 3.7 years (p < .0001) and a trend for overall survival. The addition of rituximab to CHOP was updated at ASH 2008, and continued benefits in PFS (32 months versus 65 months, p < .0001) and five-year overall survival (84% vs. 90%, p = .049) at the five-year follow-up of the 552 randomized patients were reported. In the setting of acute leukemias, the alkylating agent laromustine (Cloretazine, Vion) continues to be explored in a number of phase 2 and 3 trials of AML, including combinations with ara-C and idarubicin, and as a single agent in elderly patients. A small phase 2 study of decitabine demonstrated a CR of 24%, with a median time to response of three months.

The class of deacetylase inhibitors (DAC-Is) continues to create enthusiasm in the therapy of hematologic malignancies, ranging from T cell non-Hodgkin’s lymphoma to refractory Hodgkin’s disease to acute leukemias. The agents include vorinostat (Vorinza, Merck), depsipeptide (Romedepsin, Gloucester), valproic acid, MGCD0103, and LBH589 (Panobinostat, Novartis), among others. Results from clinical trials are encouraging. A study of vorinostat in 31 second-line AML patients resulted in two CRs, and another CR was observed in a small 12-patient trial with Romedepsin. Vorinostat is already approved for the treatment of T cell lymphomas, and the DAC-Is have shown interesting responses alone and in the combination therapy of a variety of patients with hematologic diseases.

The future is promising for the therapy of these blood disorders, and continued improvements in understanding the molecular basis of these diseases will help direct the development of new agents.

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